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10/084,095	02/28/2002	Balazs Sumegi	1060-0144P	8470

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EXAMINER
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SPIVACK, PHYLLIS G

ART UNIT	PAPER NUMBER
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1614

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

10/084,095

Applicant(s)

SUMEGI, BALAZS

Examiner

Phyllis G. Spivack

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on 14 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-3, 6, 7 and 10-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 6, 7, 10-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

### Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

Applicant's Reply under 37 CFR 1.111 filed October 14, 2003 is acknowledged. New claim 20 is presented. Accordingly, claims 1-3, 6, 7 and 10-20 are now under consideration.

The elected species, O-(3-piperidino-2-hydroxy-1-propyl)-nicotinic acid amidoxime (compound L), in combination with the specific pyrimidine derivatives fluorouracil, floxuridine, idoxuridine, doxifluridine, cytarabine, gemcitabine, ancitabine, carmofur and tegafurin in methods for reducing the side effects in a patient receiving treatment for a tumor, as previously indicated, is free of the prior art. The search has been extended to include other compounds of instant formula I wherein any carbocycle may be present.

In the last Office Action claims 1, 3, 6 and 11-18 were rejected under judicially created doctrine as being drawn to an improper Markush group. It was asserted lack of unity of invention exists since a common nucleus among the various derivatives of **formula I** is absent when a heterocyclic moiety is encompassed within the structure.

Applicant argues the only Markush group is that recited in claims 1 and 6 are with respect to pyrimidine derivatives. While it is clear the pyrimidine derivatives satisfy the two-part Markush group for unity of invention under MPEP 803.02 because the compounds share a common utility and share a substantial structural feature disclosed as being essential to that utility, the same reasoning does not apply to the compounds of instant formula I when a heterocyclic moiety is encompassed within the structure.

Applicant's arguments are not found persuasive and the rejection of record that claims 1, 3, 6 and 11-18, and now extended to include new claim 20, are drawn to an improper Markush group is maintained. Lack of unity of invention exists because a common nucleus among the various derivatives of formula I is absent when a heterocyclic moiety is present.

Claims 1, 3, 6 and 11-18 were rejected in the last Office Action under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Subsequent to the deletion of the term "preferably" from claim 1, this rejection of record is withdrawn.

Claims 1, 2 and 6 were rejected in the last Office Action under 35 U.S.C. 112, both first and second paragraphs, with respect to the recitation "pyrimidine derivative". Applicant has supplied a section of Goodman & Gilman directed to pyrimidine analogs to show pyrimidine derivatives are known in the prior art.

Although a derivative is a chemical substance related structurally to another substance and potentially derivable from it, and, an analog is a chemical compound structurally similar to another but differing often by a single element, in this case, Applicant's argument is persuasive. These rejections of record under 35 U.S.C. 112, both first and second paragraphs, are withdrawn.

In the last Office Action claims 1-3, 6, 7 and 10-18 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for Compound "L"

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and Fluorouracil, as disclosed in Table 6, does not reasonably provide enablement for any pyrimidine derivative with any hydroximic acid derivative.

Applicant argues a *prima facie* case of non-enablement has not been made.

Claims 1-3, 6, 7 and 10-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to pharmaceutical compositions comprising pyrimidine derivatives having antitumor effect and a compound of instant formula I for reducing the side effects experienced by the patient requiring treatment for a tumor. The specification provides support for the a reduction in toxicity following administration of cisplatin (or fluorouracil) and compound L to the Sp-2 mouse myeloma cell line culture and an increase in the tumor growth inhibitory effect of cisplatin following the administration of compound L in an S-180 sarcoma cell line.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

- 1) the quantity of experimentation necessary
- 2) the amount of direction or guidance provided
- 3) the presence or absence of working examples
- 4) the nature of the invention
- 5) the state of the art

- 6) the relative skill of those in the art
- 7) the predictability of the art and
- 8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to reduction of any side effect experienced by a patient requiring treatment for any tumor comprising administering combination therapy of an antitumor pyrimidine and a compound of instant formula I.

The relative skill of those in the art is generally that of a Ph.D. or M.D.

Each particular neoplastic disease has its own specific characteristics and etiology. The unpredictability observed with single agent therapy is compounded when a combination of agents is employed. The broad recitation "reduction of any side effect experienced by a patient requiring treatment for any tumor comprising administering combination therapy of an antitumor pyrimidine and a compound of instant formula I" is inclusive of many diseases that presently have no established successful therapies.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of any neoplastic disease comprising administering a plethora of compounds.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to a reduction in toxicity following administration of cisplatin (or fluorouracil) and compound L to the Sp-2 mouse myeloma cell line culture and an increase in the tumor growth inhibitory effect of cisplatin following the administration of compound L in an S-180 sarcoma cell line.

The quantity of experimentation necessary

Applicant has failed to provide guidance as to which particular pyrimidine derivatives in combination with which particular hydroximic acid derivatives would be preferred for treatment of the many other neoplastic diseases encompassed in the claim language, besides myeloma or sarcoma. The skilled artisan would expect the interaction of a particular combination of drugs in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding nor any criteria for extrapolating beyond the combination of cisplatin (or fluorouracil) and compound L. Absent reasonable *a priori* expectations of success for using a particular chemotherapeutic combination to treat any particular neoplastic disease, one skilled in the oncology art would have to test extensively many combinations of derivatives to discover which particular disease state responds to that particular combination of compounds. Since each prospective embodiment, as well as

future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

The disclosure is objected to for the following informality: The recitation in claims 1 and 6 "known active substance" is relative in definition.

Appropriate clarification is required.

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Phyllis G. Spivack at telephone number 703-308-4703.

Phyllis G. Spivack  
Primary Examiner  
Art Unit 1614

December 28, 2003

*Phyllis Spivack*  
**PHYLLIS SPIVACK  
PRIMARY EXAMINER**